85 ~~93~~. (New) The method of claim 21, wherein the area of interest comprises a morphologically defined region of a tumor.

86 ~~94~~. (New) The method of claim 21, wherein the area of interest comprises a cell structure.

REMARKS

The Office Action mailed December 5, 2001, has been reviewed and carefully considered. Claims 1, 9, 12, 14, 16 and 43 have been amended for purposes of clarity. Claims 23 and 25 have been amended to provide correct antecedent basis. Claim 50 has been amended to delete prostate and bladder cancer, now recited in new claim 86. Claim 43 also has been amended to include additional subject matter. Support for clause (f) in claim 43 is found in the specification in Example 11 on page 41 and at page 23, lines 16-19. Support for clause (g) in claim 43 is found in the specification at page 23, lines 20-25, page 35, lines 24-35, and page 43, lines 9-11. Support for clause (h) is found in the specification at page 16, lines 33-35, page 27, lines 13-15, and page 36, lines 1-2. Support for clause (i) is found in the specification, for example, at page 6, lines 14-16, and in Example 8 at page 34. Support for new claim 87 is found in the specification, for example, at page 11, line 36 – page 12, line 7. Support for new claim 88 is found in the original claims filed in the PCT application of which the present application is a national stage application. Support for new claim 89 is found in the specification, for example, at page 16, lines 4-5, page 14, lines 14-18, and Example 14 on page 44. Support for new claim 90 is found in the specification at page 13, line 35 – page 14, line 1, and Example 11 on page 41. Support for new claims 91 and 93 is found in the specification at page 34, lines 27-29, and page 29, lines 34-35. Support for new claims 92 and 94 is found in the specification in Example 2 at page 24. Entry of these amendments is respectfully requested.

Restriction Requirement under 35 U.S.C. §§ 121 and 372

Claims 1-85 are subject to a restriction requirement because a single general inventive concept is lacking under PCT Rules 13.1 and 13.2 since the subject matter of claim 1 is allegedly

anticipated by Stapleton et al. Applicants hereby affirm election of Group I, claims 1-22 and 24-52. It is respectfully submitted that the restriction requirement should be reconsidered and withdrawn since Stapleton et al. does not anticipate claim 1 as explained below.

Rejections under 35 U.S.C. § 112, second paragraph

Claims 2, 6, 7 and 16-22 are rejected due to the alleged indefiniteness of the phrase "elongated sample." It is clear from the disclosed examples that samples extracted from the donor specimen may be elongated in certain embodiments of the method (see, e.g., the present specification at page 5, lines 5-9; page 12, lines 1-3). Whether the donor specimen itself is elongated or the elongated shape is formed during boring is not material to the ultimate shape of the extracted sample. Thus, it is the shape of the sample as extracted and placed into the recipient array that is recited in claims 2, 6, 7 and 16. Samples from non-solid tissues or tumors can also be elongated by forming solid objects from the tissue or tumor. For example, cell pellets can be formed and embedded in a paraffin block as described in the specification at page 46, lines 4-18. Moreover, there are embodiments of the disclosed methods that describe analyzing liquid samples that do not involve forming an elongated sample. For example, the specification at page 47, lines 3-5, describes pipetting a liquid cellular suspension into a matrix. Thus, there are claims that do not recite forming an elongated sample (see, e.g., claims 1 and 32). The elongated samples also may have any circumferential shape. The claims should not be limited to a particular shape since there is nothing in the specification or claims that would have led a skilled artisan to such a conclusion.

Claims 31 and 34 allegedly recite improper Markush language since they do not employ the phrase "from the group consisting essentially of." It is submitted that under current practice this phrase is not required and alternative phrases such as those in claims 31 and 34 may be used (see MPEP § 2173.05(h)(I)). Indeed, MPEP § 2173.05(h)(I) explicitly condones language of the form "wherein R is A, B, C or D."

Claims 9, 12 and 14 stand rejected for the alleged indefiniteness of the phrase "clinical and/or laboratory characteristic." Claims 9, 12 and 14 have been clarified by deleting "laboratory" since "clinical characteristics" is inclusive of characteristics that may be obtained from laboratory analysis such as node status. The clinical characteristics are not obtained from

an analysis of the specimens in the array itself, but instead are correlated with the results obtained from the biological analysis of the specimens in the array. For example, Figure 12 illustrates one conceptual approach for visually organizing the data from the biological analyses so that it can be quickly compared to clinical data regarding the specimen (page 15, line 28 – page 16, line 24). The specification provides examples of various types of clinical characteristics such as patient demographics (e.g., age and sex on page 16, lines 4-5), patient history data, clinical staging data (e.g., tumor size and tumor progression on page 14, lines 14-18), and follow-up data (e.g., relapse and survival in Example 14 on page 44). Thus, a skilled artisan reading these examples and appreciating that other clinical information may also be useful is sufficiently apprised of the meaning of "clinical characteristics."

Claims 43-48 have been rejected for reciting "a use without any active, positive steps." Claim 43 has been amended to positively recite "further comprising analyzing the results of the biological analyses." Accordingly, the pending 35 U.S.C. § 112, second paragraph rejection of claims 43-48 should be withdrawn.

Rejection under 35 U.S.C. § 101

Claims 43-48 also have been rejected under 35 U.S.C. § 101 for reciting "a use, without setting forth any steps involved in the process." Claim 43 has been amended to positively recite "further comprising analyzing the results of the biological analyses." Accordingly, the pending 35 U.S.C. § 101 rejection of claims 43-48 also should be withdrawn.

Rejection under 35 U.S.C. § 102

Claims 1, 3, 4, 10-15, 24-29, 32-42 and 49-52 have been rejected under 35 U.S.C. § 102(e) as reciting subject matter allegedly anticipated by Stapleton et al. It is respectfully submitted that Stapleton et al. is not entitled to an effective reference date that is prior to the effective priority date of the present application with respect to at least claims 1-23, 29 and 49-52. Thus, Stapleton et al. is not available as a reference under 35 U.S.C. § 102(e) with respect to at least claims 1-23, 29 and 49-52. The remaining claimed subject matter (claims 24-28 and 32-42) rejected under § 102(e) is not disclosed in the Stapleton et al. patent.

A. The Stapleton et al. patent is not available as a reference against at least claims 1, 3, 4, 10-15, 29 and 49-52.

The presently pending claims listed below in Table 1 are entitled to priority of U.S. Provisional Application No. 60/075,979 filed February 25, 1998 (referred to herein as the "'979 priority application"). A copy of the '979 priority application is appended herewith as Exhibit A for the Examiner's convenience.. Support in the '979 priority application for the claims is outlined below in Table 1. The omission of several presently pending claims from Table 1 is not an admission that the omitted claims are not supported in the '979 priority application.

Table 1

Presently pending claims	Support in the '979 priority application
1	Claim 1; Description of various biological tests on page 4, lines 21-23, page 5, lines 1-5, page 12, line 14- page 16, line 22; Examples 1-4
2	Claim 2
3	Claim 12
4	Claim 9
5	Description of the fixed tumor specimens at page 12, lines 3-5; page 25, lines 17-22
6	Claim 3; Description of sectioning the array at page 11, lines 25-29
7	Claim 4
8	Claim 5
9	Claim 6
10	Description of performing different analyses at page 4, lines 15-17
11	Claim 7
12	Claim 8
13	Claim 9
14	Description of clinical characteristics at page 13, lines

Presently pending claims	Support in the '979 priority application
	16-22
15	Description of consecutive array section at page 12, lines 5-7
16	Claim 10; Description of elongated samples at page 5, lines 13-16; Description of transverse sectioning of the arrays at page 11, lines 25-29
17	Claim 11
18	Claim 12
19	Claim 13
20	Claim 8
21	Claim 14
22	Claim 15
23	Claim 16
29	Description of examining biomarkers for expression at page 24, line 24 – page 25, line 5
49, 50 and 51	Description of utilizing array to analyze different stages of breast cancer progression at page 17, lines 13-17
52	Description of utilizing array to analyze many kinds of tumor types at page 27, line 30 – page 28, line 2

The non-provisional application upon which the Stapleton et al. patent matured was filed on April 14, 1998 - subsequent to the February 25, 1998 filing date of the '979 priority application. Thus, the disclosure in the Stapleton non-provisional application is not available as a reference under 35 U.S.C. § 102(e) for the claimed subject matter supported in the '979 priority application as indicated in Table 1.

The Stapleton et al. patent does claim benefit of U.S. Provisional Application No. 60/043,683 filed April 14, 1997 (referred to herein as the "Stapleton provisional application"). A copy of the Stapleton provisional application is appended herewith as Exhibit B for the Examiner's convenience. Pursuant to the USPTO's policy set forth in MPEP § 2136.03(III), the Stapleton provisional application filing date may be an effective § 102(e) reference date. However, inspection of the disclosure in the Stapleton provisional application reveals that it must fail as the critical reference date.

According to MPEP § 2136.03(IV), "in order to carry back the 35 U.S.C. 102(e) critical date of the U.S. patent reference to the filing date of a parent application, the parent application must (A) have a right of priority to the earlier date under 35 U.S.C. 120 and (B) support the invention claimed as required by 35 U.S.C. 112, first paragraph" (emphasis added). The Stapleton provisional application does not disclose the invention claimed in the Stapleton et al. patent as required under § 112, first paragraph.

The device of claim 1 of the Stapleton et al. patent requires matrix immobilization of cells and viruses present in a biological specimen "wherein the nucleic acids of cells and viruses immobilized on said matrix are detectable for the comparison of particular nucleic acid sequences in said biological specimen with another biological specimen." The Stapleton provisional application does not appear to disclose comparing the nucleic acid sequences in one biological specimen to those of another biological specimen. Detecting nucleic acid sequences in a single biological specimen is disclosed in the Stapleton provisional application, but there is no mention of comparing the detected sequences to other sequences from a different biological specimen. It follows that the Stapleton provisional application does not satisfy at least the written description and enablement requirements of 35 U.S.C. 112, first paragraph.

For the foregoing reason alone, the pending § 102(e) rejection of claims 1, 3, 4, 10-15, 29 and 49- 52 should be reconsidered and withdrawn. In addition, the relevant disclosure in the Stapleton et al. patent relied upon as supporting the rejection under § 102(e) of claim 1 does not appear in the Stapleton provisional application.

In particular, column 14, lines 55-66 and Figure 2 of the Stapleton et al. patent are cited in the Office Action as describing the presently recited feature in claim 1 of "placing each donor specimen in an assigned location in a recipient array." The Abstract and claim 1 of the Stapleton et al. patent are cited in the Office Action as describing the presently recited "parallel analysis" feature in claim 1 that involves "comparing the results of the biological analysis in corresponding assigned locations of different copies to determine if there are correlations between the results of the biological analysis at each assigned location." However, the Stapleton provisional application did not include Figure 2 or the description found in column 14, lines 55-66, the Abstract and claim 1 of the Stapleton et al. patent. The relevant disclosure was not present until the April 14, 1998 non-provisional application from which the Stapleton et al. patent matured. In contrast, applicants' '979 priority application clearly described the features missing from the

Stapleton provisional application (see, e.g., claim 1 in the '979 priority application). Applying the classical test from *Alexander Milburn Co. v. Davis-Bournonville Co.*, 270 U.S. 390 (1926) underpinning § 102(e), even assuming that the Stapleton provisional application could have issued as a patent on the day it was filed the resulting patent would not have anticipated presently pending claim 1 (and claims 3, 4, 10-15, 29 and 49-52 that depend from claim 1).

B. Claims 24-28 and 32-42 are not described in Stapleton et al.

Claim 24 includes "using a nucleic acid microarray to identify a biomarker to be used in a biological analysis on the recipient array." The Office Action does not indicate where Stapleton et al. might describe this presently claimed subject matter. Upon close inspection it is apparent that Stapleton et al. indeed fails to disclose the use of a nucleic acid microarray to identify a biomarker for use in a biological analysis of a donor specimen recipient array. Since claim 24 is not anticipated, it follows that claims 25-28 that depend from claim 24 are likewise not anticipated.

Claim 32 is directed to combining nucleic acid array techniques with biological specimen array techniques to obtain high-throughput efficiencies. In particular, a nucleic acid array technique can be used to screen multiple genes in a biological specimen to focus selection of a nucleic acid probe that is particularly promising for then screening multiple biological specimens using biological specimen array techniques. Alternatively to (or in conjunction with) such an approach, a biological specimen array technique can be used to screen multiple biological specimens to focus selection of a nucleic acid array that is particularly promising for detecting which genes are abnormally expressed. An example of this strategy is graphically represented in Figures 27 and 28 and described at page 6, line 28 - page 7, line 4 of the present application.

The comments at the bottom half of page 6 of the Office Action citing example 5 of the Stapleton et al. patent apparently are directed to claim 32, although the language of claim 32 is not accurately re-stated. Example 5 of Stapleton et al. describes various RNA assays performed on cells immobilized on fibrous matrices. In each assay, reverse transcriptase-immobilized sample amplification (RT-ISA) reaction systems were contacted with the cell-impregnated matrices. There is no indication that a nucleic acid array (that is, an arrangement of nucleic acid in assigned locations on a matrix) was contacted with the cell-impregnated matrices. In addition,

there is no indication that the results of the RT-ISA assays were used to select a nucleic acid array for detecting which genes are abnormally expressed. In contrast, claim 32 specifically calls for using a nucleic acid array in analyzing genetic changes or gene expression in a tissue specimen. Since claim 32 is not anticipated, it follows that claims 33-42 that depend from claim 32 are likewise not anticipated.

Rejections under 35 U.S.C. § 103

Claims 1-15, 24-30, 32-42 and 49-52 have been rejected under § 103 over Stapleton et al. combined with Furmanski et al. Stapleton et al. allegedly anticipates the subject matter of claims 1, 3, 4, 10-15, 24-29, 32-42 and 49-52 and the Office Action does not offer any reason why Furmanski et al. combined with Stapleton et al. also would have rendered these claims obvious. Accordingly, applicants understand the § 103 rejection over Stapleton et al. combined with Furmanski et al. to be directed at claims 2, 5-9, and 30.

Stapleton et al. is not available as a reference against claims 2 and 5-9 as explained above in connection with the § 102(e) reference. Thus, the Stapleton et al. patent cannot be used to support a § 103 rejection of claims 2 and 5-9. Applicants also note that the disclosure in the Stapleton provisional application could not be combined with Furmanski et al. for the reasons delineated in MPEP § 2136.03(IV)'s explanation of *In re Wertheim*, 209 USPQ 554 (CCPA 1981).

With respect to claim 30, the Examiner has not indicated where Stapleton et al. or Furmanski et al. describe or teach comparing the results of multiple immunologic analyses to determine alteration of protein expression.

Claims 1, 3, 4, 10-15, 24-29, 31-42 and 49-52 have been rejected under § 103 over Stapleton et al. combined with Leveen et al. Stapleton et al. allegedly anticipates the subject matter of claims 1, 3, 4, 10-15, 24-29, 32-42 and 49-52 and the Office Action does not offer any reason why Furmanski et al. combined with Leveen et al. also would have rendered these claims obvious. Accordingly, applicants understand the § 103 rejection over Stapleton et al. combined with Leveen et al. to be directed at claim 31.

Claim 31 specifies that one gene alteration of interest is an overexpression of PDGFB in breast, lung, colon, testicular, endometrial or bladder cancer. The work of Leveen et al. involved

examining the expression of PDGFB in a melanoma cell line. The article does state that "many human tumor cell types frequently express PDGFA and PDGFB mRNA and protein" but there is no mention of any specific type of human cell other than melanoma. Melanoma is very different from the cancers listed in claim 31. Expression of a growth factor in melanoma is not predictive of expression in other cancers. In fact, it is known that different growth factors are expressed in different cancers. Thus, there is nothing in Leveen et al. that would have suggested searching for an overexpression of PDGFB in breast, lung, colon, testicular, endometrial or bladder cancer.

Conclusion

It is respectfully submitted that the present claims are in condition for allowance. In particular, the § 102(e) and § 103 rejections should be withdrawn since Stapleton et al. either is not available as a reference or it fails to teach the claimed subject matter either alone or in combination with the other relied upon documents. Should there be any questions regarding this application, Examiner Chakrabarti is invited to contact the undersigned at the telephone number shown below.

Respectfully submitted,

KLARQUIST SPARKMAN, LLP

By William D Noonan
William D. Noonan, M.D.
Registration No. 30,878

One World Trade Center, Suite 1600
121 S.W. Salmon Street
Portland, Oregon 97204
Telephone: (503) 226-7391
Facsimile: (503) 228-9446

Marked-up Version of Amended Specification and Claims
Pursuant to 37 C.F.R. §§ 1.121(b)-(c)

The specification has been amended as follows:

Please add the following paragraph prior to line 4 on page 1:

PRIORITY CLAIM

This application was filed as a 35 U.S.C. § 371 application of PCT International Application No. US99/04000 filed February 24, 1999, which designated the United States and was published in English under PCT Article 21(2), and which in turn claims benefit of U.S. Provisional Application 60/075,979, filed February 25, 1998 and U.S. Provisional Application 60/106,038, filed October 28, 1998.

The paragraph beginning at page 8, line 26, has been amended as follows:

FIG. 26A is a schematic diagram of a breast cancer tissue microarray, as well as a digital image of a hybridization, showing that FGFR2 was amplified in 4.5% of the tumor samples in the breast cancer tissue microarray. FIG. 26B is an enlargement of a single donor specimen in the breast cancer tissue microarray.

The claims have been amended as follows:

1. (Amended) A method of parallel analysis of biological specimens, comprising:

obtaining a plurality of donor specimens;

placing each donor specimen in an assigned location in a recipient array;

obtaining a plurality of substantial copies of the recipient array in a manner that each substantial copy contains a plurality of donor specimens that maintain their assigned locations;

performing a biological analysis of each substantial copy; and

comparing the results of the biological analysis in corresponding assigned locations of different substantial copies to determine if there are correlations between the results of the biological analysis at each assigned location.

9. (Amended) The method of claim 1, further comprising associating a clinical [or laboratory] characteristic[, or both] with each assigned location in the recipient array.

12. (Amended) The method of claim 10, further comprising determining whether there are correlations between clinical [or laboratory] characteristics, associated with each assigned location, and the different biological analyses.

14. (Amended) The method of claim 12, wherein the clinical [and laboratory] characteristics are determined apart from performing the different biological analysis of each copy of the array; and

the characteristics are one or more of patient age, tumor grade, tumor size, node status, and receptor status.

16. (Amended) A method of parallel analysis of substantially identical arrays of tissue specimens, comprising:

forming a donor block comprising a biological specimen embedded in embedding medium;

obtaining a plurality of elongated donor sample cores from the biological specimen;

boring receptacle cores from a recipient embedding medium to form an array of elongated receptacles;

placing the donor sample cores in the elongated receptacles at assigned locations in the array;

sectioning the recipient embedding medium transverse to the elongated receptacles to obtain a cross-section of the donor sample cores in the array, while maintaining the assigned locations in the array in consecutive cross-sections;

performing a different biological analysis of each cross-section; and

comparing a result of each biological analysis in corresponding assigned locations of different sections to determine if there are correlations between the results of the different biological analyses at each assigned location.

23. (Amended) A cross-section of the donor sample cores obtained by the method of claim [14]16.

25. (Amended) The method of claim 24, wherein the nucleic acid [array] microarray is a cDNA or oligonucleotide microarray.

43. (Amended) The method of claim 1, [wherein] further comprising analyzing the results of the different biological analyses [are used] to:

a. evaluate a reagent for disease diagnosis or treatment;

b. identify a prognostic marker for a disease;

c. prioritize targets for drug development;

d. assess or select therapy for a disease type; [or]

e. find a biochemical target for medical therapy;

f. determine the frequency of a target in pathological and normal physiological tissue;

g. identify therapeutic targets that are expressed in pathological tissue relative to normal physiological tissue;

h. compare the expression or presence of a target at the DNA, RNA and protein level; or

i. identify, validate, and prioritize targets that are defined by utilizing bioinformatic analyses.

50. (Amended) The method of claim 49, wherein the donor specimens are [specimens] from [one or more tumors selected from the group of] breast[, prostate and bladder] cancer tumors.